UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,750	04/17/2001	James P. Elia	1000-10-C01	7239

7590 12/09/2004

Gerald K. White
GERALD K. WHITE & ASSOCIATES, P.C.
205 W. Randolph Street, Suite 835
Chicago, IL 60606

EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-203,206-236 and 238-256* is/are pending in the application.

4a) Of the above claim(s) *6-203,206-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *236, 238, 239, and 243-256* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendments received 17 February 2004 and 30 June 2004 have been entered in full. Claims 1-5, 204, 205, and 237 are canceled. Claims 6-203, 206-235, and 240-242 remain withdrawn from consideration as being directed to a non-elected invention. Claims 236, 238, 239, and 243-256 are under examination. Applicant is advised that newly submitted claims 254-256 will be examined only to the extent that they read on the elected invention; i.e., a method of growing a new portion of a pre-existing **heart** comprising placing a **cellular** growth factor in a body of a patient to grow new muscle in said **heart**.

The Information Disclosure Statements received 30 July 2004, 20 September 2004 and 21 October 2004 have been entered into the file. It is believed that these include the copies of the Information Disclosure Statements deemed to have been missing by Applicant (see comments on p. 28 of the amendment received 17 February 2004). The second supplemental declarations of Drs. Heuser and Lorincz have been entered into the file.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Comments Presented in Amendment Received 30 June 2004

Applicant argues that the holding of non-responsiveness should be reconsidered. The examiner maintains that the instant claims, directed to a method of growing a new

portion of a pre-existing heart comprising administering a cellular growth factor in a body of a human patient and growing new muscle and a new artery in said heart, correspond more closely to non-elected Group 83 rather than elected Group 79. However, in the interest of avoiding further delay in prosecution, discretion is being used to allow the Applicant to shift the elected invention to the subject matter of claims 236, 238, 239 and 243-256.

Withdrawn Objections And/Or Rejections

The rejection of claims 245, 248 and 249 under 35 U.S.C. § 112, first paragraph, regarding new matter, as set forth at p. 4 of the previous Office Action (mailed 28 November 2003) is *withdrawn in part* based on Applicant's response (received 17 February 2004). Specifically, written description has been identified for "multifactorial and non-specific cells."

The rejection of claims 204 and 205 under 35 U.S.C. § 102(b) as being anticipated by Murry et al. as s et forth at p. 10 of the previous Office Action (mailed 28 November 2003) is *withdrawn* in view of the canceled claims.

The rejection of claims 236-239, 243-247, 250, 251 and 253 under 35 U.S.C. § 103(a) as being unpatentable over Murry et al. as set forth at pp. 10-12 of the previous Office Action (mailed 28 November 2003) is *withdrawn* in view of the canceled and amended claims.

The rejection of claim 252 under 35 U.S.C. § 103(a) as being unpatentable over Murry et al. in view of Nabel et al. as set forth at pp. 12-13 of the previous Office Action (mailed 28 November 2003) is *withdrawn* in view of the amended claims.

35 U.S.C. § 112, First Paragraph

A) New Matter: Claims 248, 249 and 252 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This new matter issue is in regard to support for intravenous injection of cells, intraluminal injection of cells and angioplasty delivery of cells. The basis for this rejection can be found at p. 4 of the previous Office Action (mailed 28 November 2003). It is noted that claim 252 was inadvertently left out of the original rejection. However, it is clear that this was a mere typographical error, since claim 252 was the only claim reciting angioplasty delivery, which was thoroughly discussed in the original rejection.

Applicant's arguments (pp. 29-30, amendment received 17 February 2004) have been fully considered but are not found to be persuasive for the following reasons. Applicant refers to p. 45 of the specification as providing support for "intravenous injection of cells," "intraluminal injection of cells," and "angioplasty delivery of cells." Applicant refers to MPEP § 2163.02 as setting forth that it is not necessary to literally describe the subject matter of the claims. In this section of the MPEP is cited Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Applicant asserts that one skilled in the art would have understood that Applicant was in possession of the

concept of delivering cells into a patient intravenously, intraluminally, or via angioplasty. However, page 45, lines 13-16, of the specification reads as follows:

"VEGF **proteins** can be made in a lab and injected into a patient intravenously, intraluminally or intramuscularly to promote the growth of a new artery. Or, the **genes (or other genetic material**) can be applied with an angioplasty balloon, with the assistance of a vector, or by any other method." (emphases added)

Clearly, this section of the specification is limited to use of proteins or nucleic acids (genes or genetic material). Regarding "intravenous" and "intraluminal" delivery, this section of the specification is limited to the suggestion of administering a protein. Nowhere else in the specification is it suggested that cells should be administered intravenously or intraluminally. Regarding angioplasty delivery, the second sentence quoted above is limited to the suggestion of administering genes or other genetic material by angioplasty balloon. The specification defines "growth factors" as comprising cells, but does not define "genetic material" as comprising cells. For example, p. 31, lines 11-13, of the specification states "...the genetic material comprises comparable artificially produced genes, or genes harvested from other human beings or animals." Page 32, lines 8-9 state "genetic material can comprise comparable artificially produced genes or genes removed from another animal or otherwise generated." Page 35, line 4 clearly distinguished between growth factors (defined as encompassing cells) and genetic material: "genetic material plus growth factor(s) are implanted..." Page 35, lines 12-14 state "Genetic material is well conserved in nature. The Drosophila eyeless gene (ey), the mouse small ey gene (pax-6), and the Aniridia gene in humans are all homologous." Page 36, lines 25-26 state "Genes control structure and function. A gene or a bit of genetic material may act as a master control gene..." Clearly, the

specification uses "genetic material" as pertaining to nucleic acids such as genes. It is also noted that one skilled in the art would only interpret "assistance of a vector," recited in the same sentence that uses "genetic material," as only applying to nucleic acids (genes or RNA or cDNA, etc.).

Regarding MPEP § 2163.02 and the case law cited therein: This section of the MPEP reads thus (in part):

"An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."

In the instant case, none of these criteria have been met. There was no reduction to practice, and the specification only refers to proteins, genes and "genetic material," *but not cells*, as being useful in intravenous, intraluminal and angioplasty delivery. Therefore, the rejection is maintained.

B) Enablement: Claims 248 and 249 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The basis for this rejection is set forth at pp. 4-8 of the previous Office Action (mailed 28 November 2003).

Applicant's arguments (pp. 30-37 of the amendment received 17 February 2004) have been fully considered but are not found to be persuasive for the following reasons.

Applicant refers to the supplemental declarations of Drs. Heuser and Lorincz submitted under 37 CFR 1.132 (received 17 February 2004) as providing expert medical opinions that the specification fully enables the claimed invention. The Heuser and Lorincz declarations under 37 CFR 1.132 filed 06 October 2003 and 17 February 2004 are insufficient to overcome the rejection of claims 248 and 249 based upon 35 U.S.C. § 112, first paragraph as set forth in the last Office action for the following reasons. First, while it is clear that Drs. Heuser and Lorincz are accomplished physicians, it is noted that none of the declarations (submitted 06 October 2003) or the supplemental declarations (submitted 17 February 2004) report experience with cellular therapy as required by the instant claims. Cells suitable for therapy, such as stem cells, are not like other types of drugs routinely administered in the art. They cannot simply be bought from a drug company; they have to be isolated and cultured. They cannot simply be injected; they have to be handled delicately so as to avoid mechanical or chemical rupture of the cell membranes. They do not enter cells to be effective; they must graft onto the site of injury. Thus, a specialist in cell therapy must possess skills specific to that type of therapy. Furthermore, the Heuser and Lorincz declarations submitted 06 October 2003 point to several publications as supporting their opinions, each of which are summarized in Exhibit E of each declaration. Those references pertaining to cell therapy will each be addressed. First, Strauer et al. et al. (2002, Circulation 106:913, 1918) disclose balloon catheter injection of bone marrow cells to repair a dead portion of a heart. The rejected claims pertain to intravenous and intraluminal injection only, and thus Strauer et al. et al. is not particularly relevant.

Although balloon catheter administration can be considered a species of the genus of intraluminal delivery methods, it is not commensurate in scope with the claims which read on delivery to the lumen of arteries, veins, intestines, heart chambers, lung, peritoneum, etc. Furthermore, Strauer et al. et al.'s balloon catheter administration involved infusion of the cells by high-pressure injection directly into the necrotic area, to avoid the "wash-away" effect of standard intraluminal administration (Strauer et al. et al., p. 1917, third paragraph of left column). It is noted that the specification as originally filed provides no guidance regarding high-pressure injection. Thus the post-filing date publication of Strauer et al. et al. cannot be relied upon to support enablement of the claims, as it uses methods which were not disclosed in the specification as originally filed. Additionally, Strauer et al. et al. specifically points out the shortcomings of intravenous administration of cells for heart therapy at p. 1917, second paragraph of the left column, where they state that "only a very small fraction of infused cells can reach the infarct region," "intravenous application would require many circulation passages to enable infused cells to come into contact with the infarct-related artery," and "homing of cells to other organs could considerably reduce the numbers of cells dedicated to cell repair in the infracted zone." Thus, Strauer et al. et al. specifically provides evidence of non-enablement of the instant claims reciting intravenous administration of cells.
Second, Pagani (2003, J. Am. Coll. Cardiol. 41:879-888) is described by the declarations as disclosing surgery with syringe injection of skeletal muscle cells to repair a dead portion of a heart. Only an Abstract was provided. It was impossible to judge conclusively from the Abstract how the cells were administered, although it would

appear that they may have been injected directly into the heart muscle (intramuscular administration), and thus the reference does not speak to the enablement of intravenous or intraluminal administration. Also, it is noted that the specification as originally filed provides no guidance regarding "LVAD implantation" as used in Pagani. Thus the post-filing date publication of Pagani cannot be relied upon to support enablement of the claims, as it uses methods which were not disclosed in the specification as originally filed. Third, Hamano (2001, Jpn. Circ. J. 65:845-847) is described by Applicant as disclosing surgery with syringe injection of bone marrow cells to repair a damaged portion of a heart. Again, only an Abstract was provided, from which it was impossible to judge conclusively exactly how the cells were administered. However, Hamano uses the word "implant," suggesting that the cells were placed into the heart muscle itself (intramuscular administration), and thus cannot be relied upon to support enablement of intravenous or intraluminal administration of cells as recited in the rejected claims. Fourth, Tse (2003, Lancet 361:47-49) is described by the declarations as disclosing catheter with needle injection of bone marrow cells to repair a damaged portion of a heart. Again, only an Abstract was provided, from which it was impossible to judge conclusively exactly how the cells were administered. However, Tse refers to intramyocardial (intramuscular) implantation of cells, and thus cannot be used to support enablement of the rejected claims which recite intravenous or intraluminal administration of cells. Finally, Perin (2003, Circulation, epub ahead of print) is described by the declarations as disclosing administration of bone marrow cells by catheter with needle injection to repair a damaged portion of a heart. Again, only an

Abstract was provided, from which it was impossible to judge conclusively exactly how the cells were administered. However, Perin refers to "transendocardial" injections of cells and "intramyocardial" injections of cells, both of which appear to be intramuscular forms of administration. Thus, Perin also cannot be used to support enablement of the rejected claims which recite intravenous or intraluminal administration of cells. Therefore, the opinions of Drs. Heuser and Lorincz (as they appear in the declarations of 06 October 2003 and 17 February 2004) are not found to be persuasive, as they are based upon evidence that is found to be either irrelevant, not commensurate in scope with the claims, or relying on methods which were not disclosed in the specification as originally filed.

Applicant has also submitted second supplemental declarations by Drs. Heuser and Lorincz (received 30 July 2004). The Heuser and Lorincz second supplemental declarations under 37 CFR 1.132 filed 30 July 2004 are insufficient to overcome the rejection of claims 248 and 249 based upon 35 U.S.C. § 112, first paragraph, as set forth in the last Office action for the following reasons. The second supplemental declaration of Dr. Heuser opines that Dr. Heuser is an expert interventional cardiologist and has experience in cellular therapy, referring to U.S. Patent 6,190,379 which discusses delivery of protein and/or muscle cells to the myocardium. This has been fully considered but is not found to be persuasive. Again, it is clear that Dr. Heuser is an eminent, highly accomplished cardiologist. However, in the second supplemental declaration, Dr. Heuser asserts that he has worked in gene therapy. There is no evidence to support this statement. Dr. Heuser refers to his experience with delivering

FGF into a rabbit hind limb model. However, this is administration of a protein growth factor, which has been routine in the art for some time. This therapy has no bearing on the elected invention, which is the administration of cells such as stem cells to achieve repair of dead or damaged heart tissue. Dr. Heuser refers to U.S. Patent 6,190,379 as discussing delivery of protein and/or muscle cells in the myocardium using a hot tip catheter. '379 has been reviewed but has not been found to mention delivery of any substance to the myocardium. The word "cell" does not appear in the patent. Dr. Heuser states that he is a member of the scientific advisory board for Bioheart, which is involved with "laboratory and clinical trials using skeletal muscle cultured and modified." This statement is difficult to evaluate critically, as it does not refer to any details. Also, Dr. Heuser's role in the cell delivery portion of the trials is not clear. Finally, Dr. Heuser refers to pages from the specification, indicating that it is his expert opinion that these sections would teach one skilled in the medical arts that cells are included in the disclosures. This is not found to be persuasive, as "inclusion" is not equal to an enabling disclosure. The specification has been found to be non-enabling for reasons of record. The second supplemental declaration of Dr. Lorincz states that Dr. Lorincz is familiar with stem cell technology, including bone marrow presentation. Dr. Lorincz then opines that, based on the cited pages of the specification, he believes on skilled in the medical arts would understand that cells are included in the disclosures. This has been fully considered but is not found to be persuasive. Again, it is clear that Dr. Lorincz is an eminent, highly accomplished doctor. However, the extent of Dr. Lorincz's familiarity with stem cell preparation is not defined, nor is his experience with using cells to

achieve repair of heart tissue, as required by the claims. Also, "inclusion" of a concept in a specification is not equal to an enabling disclosure. The specification has been found to be non-enabling for reasons of record.

At pp. 31-32 of the amendment, Applicant discusses in depth the publication by Strauer et al. et al. as supporting enablement of the claimed invention. Regarding Strauer et al. et al., Applicant refers to the top of p. 1913 as showing that intraluminal injection results in new artery growth and new muscle growth. Applicant argues that intraluminal injection was a well-known technique and involved no special procedures or treatments to achieve the specified results. Applicant characterizes Strauer et al. et al. as disclosing that cells can be placed in the interior of the artery and then permitted to migrate to the heart of the patient where new growth and repair occur. Applicant concludes that Strauer et al. et al. provides compelling evidence that nothing more than routine intraluminal injection is effective to achieve the results recite din the claims. This is not found to be persuasive because it is incorrect with respect to the facts. Strauer et al. et al. uses a specialized form of intraluminal delivery, specifically, balloon catheter injection with a high-pressure injection directly into the necrotic area, to avoid the "wash-away" effect of standard intraluminal administration (Strauer et al. et al., p. 1917, third paragraph of left column). Strauer et al. et al. does not disclose that the cells migrate significantly from the initial point of placement. At p. 1914, right column, Strauer et al. et al. discloses,

" ...cells were directly transplanted into the infracted zone (Figure 1). This was accomplished with the use of a balloon catheter, which was placed within the infarct-related artery. After **exact positioning of the balloon at the former infarct-vessel occlusion**, percutaneous transluminal coronary angioplasty (PTCA) was performed **6**

to 7 times for 2 to 4 minutes each. During this time, intracoronary cell transplantation via the balloon catheter was performed, using **6 to 7 fractional high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to 4 X 10^6 mononuclear cells. PTCA thoroughly prevented the backflow of cells and at the same time produced a stop-flow beyond the site of the balloon inflation to facilitate high-pressure infusion of cells into the infracted zone**. Thus, prolonged contact time for cellular migration was allowed." (emphasis added)

The specification does not provide guidance regarding the highlighted sections above. Most importantly, no mention is made of (1) high-pressure infusion of cells or (2) prevention of back-flow of cells in the specification as originally filed. Therefore, Strauer et al. et al. involves special procedures and treatments to achieve the specified results. Furthermore, Strauer et al. et al. specifically states that the "wash-away" effect of standard intraluminal administration is a short-coming and must be avoided (Strauer et al. et al., p. 1917, third paragraph of left column). It is noted that the specification as originally filed provides no guidance regarding avoidance of "wash-away" effect. Thus the post-filing date publication of Strauer et al. et al. cannot be relied upon to support enablement of the claims directed to *intraluminal* administration, as it uses methods which were not disclosed in the specification as originally filed. Additionally, Strauer et al. et al. specifically points out the shortcomings of *intravenous* administration of cells for heart therapy at p. 1917, second paragraph of the left column, where they state that "only a very small fraction of infused cells can reach the infarct region," "intravenous application would require many circulation passages to enable infused cells to come into contact with the infarct-related artery," and "homing of cells to other organs could considerably reduce the numbers of cells dedicated to cell repair in the infracted zone." Thus, Strauer et al. et al. specifically provides evidence of non-enablement of the

instant claims reciting intravenous administration of cells. Finally, it is noted that the Strauer et al. disclosure, limited to a very specialized form of intraluminal administration (i.e., balloon catheter infusion at high pressure) is not commensurate in scope with the claims which recite any form of intraluminal or intravenous administration.

Applicant refers to the publication by Deb et al. (2003, Circulation 107:1247) as establishing that human bone marrow can be used as a source of extracardiac progenitor cells capable of *de novo* cardiomyocyte formation. Bone marrow transplants are administered intravenously, as argued by Applicant (a fact not contested by the Examiner). Applicant concludes that little, if any, experimentation is required to use such common administration techniques, since intravenously administered cells can migrate to the human patient's heart without special treatments or procedures. This has been fully considered but is not found to be persuasive. There is no doubt that Deb et al. provides evidence that bone marrow cells, administered intravenously, can migrate to the heart. However, this alone does not achieve the results required by the claims, i.e., repairing a dead or damaged portion of a heart. Deb et al. discloses that only 0.23 $\pm$ 0.06% of the cardiomyocytes were from the transplanted cells. Such numbers of cells are greatly insufficient to achieve the effects required by the claims. As evidence of this, Strauer et al. administered 6 to 7 fractional high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to 4 X 10^6 mononuclear cells directly to the infarct site in order to achieve their effects. In fact, Strauer et al. specifically points to shortcomings of intravenous administration at p. 1917, as discussed above. The evidence as a whole indicates that intravenous administration of cells to repair a dead

or damaged portion of a heart has not yet been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them from re-migrating away from the site. As this problem has not yet been solved in the literature, and no suggestions for solving the problem are suggested in the specification as originally filed, undue experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result.

Applicant next addresses the Wands factors discussed in the rejection. Regarding quantity of experimentation and the amount of guidance or direction provided by the specification, Applicant argues that little experimentation would have been needed, referring to the Heuser and Lorincz supplemental declarations, and the Strauer et al. and Deb et al. publications, as evidence of such. Applicant argues that this evidence indicates that, following administration of the cells, the body is believed to cause the cells to naturally migrate to the heart and achieve the claims' results, thus obviating the need for large amounts of experimentation. This has been fully considered but is not found to be persuasive. The Deb et al. publication is the only evidence that addresses administration of cells at a site other than exactly at the infarct zone. Deb et al. clearly indicates that very few intravenously-administered cells (0.23 $\pm$ 0.0% of total cardiomyocytes) travel to the heart. Such is not sufficient to achieve the effects required by the claims. As evidence of this, Strauer et al. administered 6 to 7 fractional high-pressure infusions of 2 to 3 mL cell suspension, each of which contained 1.5 to 4 X 10^6 mononuclear cells directly to the infarct site in order to achieve their effects. In fact, Strauer et al. specifically points to shortcomings of intravenous

administration at p. 1917, as discussed above. The evidence as a whole indicates that intravenous administration of cells to repair a dead or damaged portion of a heart has not yet been achieved due to the obstacles involved with getting sufficient numbers of cells to the dead/damaged site and preventing them from re-migrating away from the site. As this problem has not yet been solved in the literature, and no suggestions for solving the problem are suggested in the specification as originally filed, a great quantity of experimentation would be required of the skilled artisan to practice the claimed method to achieve the required result.

Regarding working examples, Applicant argues that there is no legal or administrative requirement that a patent application contain working examples. Applicant argues that the Strauer et al. and Deb et al. publications provide evidence of the invention's operability and thus the absence of working examples in the specification is of little or no weight. This has been fully considered but is not found persuasive. The deficiencies of the Strauer et al. and Deb et al. publications have been discussed above. In view of this, the lack of working examples in the specification must be taken into consideration, as provided for in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Regarding the complexity of the invention, Applicant argues that Murry et al., cited by the examiner, does not speak to the complexity of intravenous and intraluminal techniques in the context of heart repair. Applicant argues that the invention is directed to repairing a heart after damage, rather than limiting damage immediately following a heart attack. This has been fully considered but is not found to be persuasive. Murry et

al. was cited as showing that treatment of heart damage following myocardial infarction is complex, regardless of what techniques are used to treat. Moreover, Strauer et al. specifically discusses the complex problems associated with intravenous administration of cells, and illustrates the complexity of one type of intraluminal administration (i.e., balloon catheter administration using high pressure infusion). Finally, it is noted that Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), found that a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). In the instant complex case, no working embodiments were given.

Regarding the state of the art, Applicant argues that the publications cited by the examiner are not pertinent or all inclusive since none of the publications treat humans. Applicant reasons that the conclusions or inferences drawn from such publications are flawed. Applicant also argues that the fact that the publications involve intramuscular administration does not mean that other types of injections would be inoperative. Applicant again refers to Strauer et al. et al. and Deb et al. as providing evidence that intravenous and intraluminal administration are also effective for treating humans. This has been fully considered but is not found to be persuasive. The papers cited in the previous Office Action used model systems and involved research done clearly for developing treatments for humans. Thus, the conclusions and inferences drawn in

these publications are directly on point regarding the state of the art. Furthermore, since the majority of the publications form this time were geared toward intramuscular administration rather than intravenous or intraluminal administration techniques, it is clear that the state of the art favored intramuscular administration over intravenous or intraluminal administration. Such speaks to the state of the art and is relevant evidence to be considered when making a determination of whether undue experimentation would have been required by one skilled in the art at the time of the invention.

Regarding unpredictability, Applicant argues that the examiners' concerns are unfounded in view of the evidence that intravenous and intraluminal injection are effective. This is not found to be persuasive in view of the deficiencies of the "evidence" brought forth by Applicant, as discussed in depth above.

Regarding the breadth of the claims, Applicant argues that no details of intravenous or intraluminal administration are required in the claims, since the respective techniques are well-known in the art and do not require specialized treatments or procedures to be effective. Applicant believes dosages are not required. Applicant believes targeting molecules need not be specified as such speak to the mechanism of the invention, which Applicant is not required to explain. Applicant asserts that the disclosure of the novel method and results constitutes an enabling disclosure. This has been fully considered but is not found to be persuasive. As has been argued above, although intravenous and intraluminal administration of certain drugs for certain effects may be routine, but intravenous and intraluminal administration of cells to repair dead or damaged heart tissue was not well-known in the art.

Furthermore, Strauer et al. et al. and Deb et al. provide evidence that intravenous and intraluminal administration fail to deliver sufficient cells to the site of damage to achieve the required result. However, all of these details are off-point to the issue of the breadth of the claims. This Wands factor (i.e., the breadth of the claims) merely takes into account what the claims does and does not encompass. The claims merely recite intravenous or intraluminal administration, and do not provide any other limitations (e.g., which veins, which lumens, how many cells, any other substances administered, etc.). Therefore, the breadth of the claims is very large, a factor which is to be taken into account when making the determination of whether or not the amount of experimentation required by the skilled artisan to practice the claimed invention in its full scope is or is not undue.

Applicant concludes that 35 U.S.C. § 112, first paragraph, only requires objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. Referring to case law, Applicant argues that the specification need only teach the skilled artisan how to make and use the claimed invention. Applicant again refers to the Heuser and Lorincz supplemental declarations, as well as the Strauer et al. et al. and Deb et al. publications, as providing evidence of enablement. This has been fully considered but is not found to be persuasive. While the examiner takes no issue with Applicant's interpretation of the case law, the evidence submitted by Applicant in the response does not shift the balance of the evidence as a whole to support enablement of the claimed invention, for reasons discussed above. Due to the large quantity of experimentation necessary to

determine how to administer cells intravenously or intraluminally to achieve repair of a distant dead or damaged heart portion, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of targeting cells to a distant site, and the breadth of the claims, it is determined that undue experimentation would have been required of the skilled artisan to practice the claimed methods.

35 U.S.C. § 112, Second Paragraph

Claim 254 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at pp. 8-9 of the previous Office Action (mailed 28 November 2003).

Applicant's arguments (p. 37, amendment received 17 February 2004) have been fully considered but are not found to be persuasive for the following reasons.

Applicant points to p. 37 of the specification as providing a definition. This is not found to be persuasive. Page 37 of the specification states, "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." While this sentence provides examples of what the term encompasses, it does not provide an unambiguous definition. The functional portion of the definition, "...provide[s] the necessary in vivo and in vitro cascade of

genetic material ..." makes no sense. What is a cascade of genetic material? Neither the specification nor the art clearly defines these terms.

Applicant concludes that the term is used to define cellular material that can differentiate and possess homing/migration characteristics. This is also not found to be persuasive. It is not clear on what Applicant is relying to come to this conclusion. The specification never uses the terms "migration" or "homing."

Priority

The effective filing date of the instant application is deemed to be 21 April 1998 for reasons of record.

Applicant argues (pp. 38-39, amendment received 17 February 2004) that pp. 20-21 and 30-31 of the instant specification demonstrate that Applicant had possession of the instantly claimed subject matter. Applicant argues one skilled in the art would understand that "mesodermal tissue" includes arteries and muscle, and "soft tissue" or "skeletal tissue" includes heart. This has been fully considered but is not found to be persuasive. To receive benefit of an earlier filing date under 35 U.S.C. § 120, the parent application's specification must provide an enabling disclosure of the subject matter claimed in the child. Such is not the case here. "Inclusion" of a concept is not evidence of enablement. The courts have stated that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997). The courts have also stated that "[t]ossing out the

mere germ of an idea does not constitute an enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech Inc. v. Novo Nordisk A/S, *supra*).

NEW REJECTIONS

35 U.S.C. § 102

Claims 254 and 255 are rejected under 35 U.S.C. 102(b) as being anticipated by Murry et al. (1996, J. Clin. Invest. 98:2512-2523).

Murry et al. teach a method of growing a new portion of a pre-existing heart comprising placing a cellular growth factor in a body of a patient to grow new muscle in said heart. See Results and Discussion sections, and Figure 1, showing new muscle growth in the heart.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 236, 238, 239, 243-253 and 256 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims have been amended to recite growth of new *cardiac* muscle. and formation of a "new" artery.

The courts have determined several factors to be considered in making a determination of whether or not undue experimentation would have been required of the skilled artisan to make and use the claimed invention (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). These are:

1) quantity of experimentation required,

2) amount of direction/guidance presented in the specification,

3) presence or absence of working examples,

4) nature of the invention,

5) state of the prior art,

6) level of skill of those in the art,

7) predictability, and

8) breadth of the claims.

1) In the instant case, the quantity of experimentation required would be very large. Applicant's attention is directed to pp. 1916 to 1918 of Strauer et al. (of record), who review the crucial questions that had to be addressed while designing and realizing their trial of administering stem cells to human patients to repair damaged heart tissue. These included decisions regarding what cell population to use, what delivery method to use, and when cells should be transplanted. As can be seen from pp. 1916-1918, these were not simple or routine matters and involved great quantities of experimentation. In fact, one can see that the determinations of these details involved the act of invention. Furthermore, despite all of this work, growth of new *cardiac* muscle was not achieved. The instant specification has not provided guidance for one skilled in the art to

determine how to grow new cardiac muscle without resorting to large amounts of trial and error experimentation.

2) The specification provides no guidance along the lines of the details worked out by Strauer et al. The specification broadly asserts that the administration of cells can achieve diverse effects, including growth of any "hard" tissue or "soft" tissue (p. 20), formation of entire new organs (p. 32) or portions of organs (p. 46), restoration of function in any organ (p. 47), formation of auxiliary organs (p. 49), correction of necrosis (p. 49), replacement of missing limbs or body parts (p. 50), treatment of inflammation (p. 50), correction of musculoskeletal injuries or deficiencies (p. 50), formation of hybrid organs (p. 50), etc. No guidance or details are provided as to *how* to achieve these remarkable effects, most of which have never been achieved in this art to this day. The courts have stated that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 (1997). The courts have also stated that "[t]ossing out the mere germ of an idea does not constitute an enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention" (Genentech Inc. v. Novo Nordisk A/S, *supra*).

3) The specification contains only prophetic examples. In fact, none of the prophetic examples are directed to administration of cells to grow cardiac muscle or a new artery. Therefore, there are no examples, working or prophetic, directed to the elected invention.

4) The nature of the invention is highly complex, as evidenced by all of the publications of record, including Strauer et al. All inventions involving administration of active agents of any kind to a patient to achieve a physiological reaction are complex, as evidenced by the fact that medical professionals who practice such methods must endure years of study and training before being certified to attempt such procedures on human patients.

5) The state of the art does not support the specification's (and claims') assertion that cardiac muscle and a new artery can be grown. None of the numerous post-filing date publications put on the record by Applicant to support enablement of the claimed invention report the *de novo* growth of an artery as defined by Applicant, including Strauer et al. In fact, it is noted that as late as April of 2004, there were reports that bone marrow stem cells do not, in fact, contribute to myocardial regeneration (i.e., growth of cardiac muscle). See Balsam et al. (2004, Nature 428:668-673), who report that hematopoietic stem cells were directly injected into ischemic myocardium but they expressed hematopoietic markers rather than cardiac tissue-specific markers. Regarding formation of new arteries, recent reports have shown that when bone marrow stem cells are administered, new blood vessels form because of angiogenic factors released by the cells; the cells themselves do not differentiate into the cells that make up the blood vessels. See Balsam et al. (2004, Nature 428:668-673) and Ziegelhoeffer et al. (2004, Circulation Research 94:230-238).

6) The level of skill in the art is admittedly high.

7) The invention is unpredictable, as it involves administering active agents to a living patient to achieve a physiological response. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), most chemical reactions and physiological activity involve unpredictable factors. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

8) The breadth of the claims is quite large. The elected invention is directed to a method of administering any type of cell to an undefined area of the body of a human patient to grow new cardiac muscle and a new artery (of any type or location).

Due to the large quantity of experimentation necessary to determine how to effectively administer cells to achieve growth of a new cardiac muscle and formation of a new artery, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the effects of an agent on a physiological response, and the breadth of the claims which fail to recite limitations regarding cell type or dosage or site of delivery, etc., undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Title

Due to the amendment of the claims, the title of the invention is no longer descriptive. A new title is required that is clearly indicative of the invention to which the

claims are directed. The following is suggested: METHOD OF GROWING MUSCLE AND AN ARTERY IN A HUMAN HEART.

Conclusion

No claims are allowed.

This application contains claims 6-203, 206-235, and 240-242 drawn to an invention nonelected with traverse in elections received 06 October 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER